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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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BIRCH STEWART KOLASCH & BIRCH PO BOX 747 FALLS CHURCH, VA 22040-0747			MYERS, CARLA J	
			ART UNIT	PAPER NUMBER
			1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/695,744	PATERLINI-BRECHOT, PATRIZIA	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-29 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-29 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 03 November 2004 and 30 October 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>2/12/04</u> . | 6) <input checked="" type="checkbox"/> Other: <u>Notice to Comply</u> . |

DETAILED ACTION

Specification

1. The specification is objected to because at page 19 the title "Key to Figures" should be amended to read "Brief Description of the Drawings." See 37 CFR 1.74.
2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821-25 because a paper and CRF copy of a Sequence Listing has not been filed including the sequences recited on page 22 of the specification. As the sequence disclosures in this application are not pertinent to the claimed invention and in the interest of compact prosecution, this case has been examined on the merits. However, in response to this Office action, Applicants must comply with the requirements of 37 CFR 1.821-1.825. In particular, Applicant is required to submit a new CRF and paper copy of the Sequence Listing containing the additional sequence, an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOs into the appropriate pages of the specification and a letter stating that the content of the paper and computer readable copies are the same.

Claim Objections

3. Claims 9-18 and 20-25 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim may not depend from another multiply dependent claim. See MPEP § 608.01(n).

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4. Claim 24 is objected to over the recitation of " 5×10^4 to 5×10^5 pores/m²" because it appears that the claim should read " 5×10^4 to 5×10^5 pores/cm²". See, for example, the teachings in the specification at page 9, wherein it is stated that "(p)referably, the filter has substantially cylindrical pores with a diameter of about 8 μ m and a density in the range of " 5×10^4 to 5×10^5 pores/cm²".

Alternatively, if the claim is intended to refer to "pores/m²", " then the specification is objected to as failing to provide proper antecedent basis for this claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o).

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 26-29 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-25 are indefinite over the recitations of "in particular" and "particularly." These phrases render the claims indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d). For example, it is unclear as to whether the claims are intended to be limited to concentrating any of the circulating cells or concentrating only the fetal cells. It is also unclear as to what is intended to be included or excluded by "certain circulating cells" and the claims do not set forth the criteria for determining what is intended to be encompassed by the "certain circulating cells."

Claims 1-25 are indefinite over the recitation of "certain enriched cells." While the claims previously refer to a step of concentrating cells, the claims do not do include a specific step of enriching cells. Thereby, it is unclear as to whether the enriched cells are the same or different from the concentrated cells. It is also unclear as to how the limitation of "certain enriched cells" is intended to further limit the claims because the claims do not clearly set forth how to select the "certain" cells.

Claims 1-25 are indefinite over the recitation of "identifying genetic anomalies specifically targeted to individually analyze cellular genomes for which a foetal origin has been demonstrated" because it is not clear as to what is intended to be meant by this phrase. It is unclear as to what the genetic anomaly targets and it is unclear as to what is encompassed by a genetic anomaly targeted a genome. For example, it is

unclear as to whether the genetic anomalies are specifically present in fetal cells or if the genetic anomalies are specific to individual cellular genomes.

Claims 2-18 and 20-25 are indefinite over the recitation of "seeking genetic markers characteristic of foetal cells" because it is not clear as to what is meant by this phrase and it is unclear as to how this phrase further limits the claims. For instance, it is unclear as to whether the claims include a general method step of identifying new fetal cell markers or if the claims are intended to include an additional step in which the cells are analyzed for fetal cell specific markers. Similarly, claims 17 and 20-25 are indefinite over the recitation of "seeking the genome of said collected cells."

Claims 4-18 and 20-25 are indefinite over the recitation of "the filtration membrane" because this phrase lacks proper antecedent basis. While the claims previously refer to a filter, the claims do not previously refer to a filtration membrane.

Claims 8-18, 20-25 are indefinite over the recitation of "genetic markers or of polymorphism, of a combination of said markers" because it is not clear as to how the recitation of the combination of markers further limits the claims or relates to the remainder of the claims. The claims are also indefinite over the recitation of "or of a particular allele assay of said markers" because it is not clear as to whether the claims are intended to include a step of performing an allele assay or whether the claims include a step of identifying a marker that was found/identified in a "particular allele assay of said markers." It is also unclear as to how the steps of detecting a marker or polymorphism by themselves demonstrate the biparental contribution of the fetal DNA.

Similarly, claims 17 and 20-25 are indefinite over the recitation of "on allele assay of said markers distinguished from those detected on the genome of non maternal cells."

Claims 9-18 and 20-25 are indefinite because it is not clear as to what is intended to be meant by a genetic or chromosomal anomaly being "carried out by identifying a genetic target."

Claims 18 and 20-25 are indefinite over the recitation of "and of a preamplified DNA preparation of cells of maternal origin or non foetal reference cells" because it is not clear as to how this recitation further limits the claims.

Claims 19-25 are indefinite because it is not clear as to how the recitations set forth in these claims relate to the remainder of the claim since the claim is not drawn to and does not previously refer to a method of determining the sex of a fetus. It is also unclear as to what is intended to be meant by "chromosomal anomaly of the gender to be detected on the genome of cells."

Claim 25 is indefinite over the recitation of "pore size of which is graded." The specification does not provide a fixed and complete definition for this phrase and there is no art recognized definition for what is intended to be encompassed by graded pore sizes. The specification (page 9) states that "the filter used is graded so that all the pores have a substantially identical diameter." Thereby, it appears that "graded" filters are intended to include filters that are calibrated or controlled so that they have pores of substantially the same size. However, the specification does not teach that the term "graded" is limited to this definition and this definition/limitation is not recited in the claims. Thereby, it is unclear as to whether graded filters are intended to refer to only

filters in which the pores are of substantially the same size, or whether graded filters include filters with pores of varying, increasing sizes (i.e. "arranged in a sequence of grades or ranks," or pores that have been ranked based on some unstated criteria. Accordingly, one cannot determine the meets and bounds of the claimed subject matter.

Claims 26-29 are indefinite over the recitations of "preferably." This phrase renders the claims indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d). For example, it is unclear as to whether the claims are intended to be limited to filters with a pore size of 6 to 15 um or to filters with a pore size of about 8 um. Similarly, claims 27-29 are indefinite over the recitation of "preferably 0.1 bars" and claims 28-29 are indefinite over the recitation of "preferably about 8 um."

Claims 26-29 provides for the use of a filtration device, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 26-29 are indefinite over the recitations of certain circulating cells because it is unclear as to which circulating cells are being referred to and it is unclear as to how one would distinguish between the certain circulating cells and the remaining circulating cells.

Claims 26-29 are indefinite over the recitations of "the upstream block" and "the downstream block" because these phrases lack proper antecedent basis since the claims do not previously refer to upstream and downstream blocks.

Claims 27-29 are indefinite over the recitation of "a ISET type filtration device" because it is not clear as to whether the ISET type filtration device is the same as or distinct from the filtration device set forth in the claims and in the later case it is unclear as to how the ISET filtration device relates to the remainder of the claims. Claims 27-29 are also indefinite over the recitation of "the applied filtration pressure" because this phrase lacks proper antecedent basis.

Claims 28 and 29 are indefinite because it is not clear as to whether the filter referred to therein is the same as or distinct from the porous filter recited in claims 26 and 17. In the later case, it is unclear as to how the second filter is utilized in the method for filtering to obtain fetal cells.

Claim 29 is indefinite over the recitation of "pore density in the range of 5×10^4 to 5×10^5 " because the claim does not set forth the units for the pore density and thereby it is unclear as to whether the density is with respect to 1 mm or 1 cm or 1 m etc.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-14, 16-17, 19-23 and 25 are rejected under 35 U.S.C. 102(a) as being anticipated by Vona (American Journal of Pathology. January 2002. 160: 51-58; cited in the IDS).

It is noted that the authorship of the Vona et al reference is distinct from the inventorship of the present application and thereby constitutes prior art by "another." Further, it is noted that Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Vona (page 52) teaches a method for prenatal diagnosis of fetal cells isolated from maternal blood wherein the method comprises:

- a) filtering a diluted sample of maternal blood through a filter according to size, in order to separate fetal cells from maternal blood cells;
- b) analyzing the cells retained on the filter by hematoxylin, eosin staining or immunohistochemical analysis and by microscopy in order to confirm the identify of the cells as being of fetal origin;
- c) performing microdissection in order to isolate and collect single fetal cells; and
- d) analyzing the collected single fetal cells to detect a genetic anomaly or to determine the sex of the fetal cells.

With respect to claim 4, Vona (e.g., page 52) teaches that microdissection is performed using a laser to cut a portion of the filter containing the cell to be collected and analyzed.

With respect to claims 7, 8 and 17, the method of Vona (pages 52-53) analyzes HLA markers and X and Y chromosomal markers. Thereby, the method of Vona allows for the demonstration of the fetal cell or maternal origin of a cell and the genotyping of a cell and the parental contribution of the fetal DNA.

With respect to claims 10-11, Vona teaches lysis of the collected single cell and preamplification of the genomic DNA (see page 52-53).

With respect to claim 12, Vona teaches that the preamplified DNA is diluted in 10ul of water and 2 ul of the preamplified DNA is used for subsequent PCR amplification reactions (i.e., about less than one fifth of the preamplified DNA preparation).

With respect to claim 13, the reference teaches sequencing the amplification products to detect genetic markers (page 52 and 53).

With respect to claim 14, the reference teaches hybridization of specific oligonucleotides to the preamplified DNA and further amplification of the fetal DNA to detect a genetic anomaly (page 52).

With respect to claim 16, Vona teaches the analysis of STR markers (page 52) and a polymorphism (see Figure 2 and pages 52-53).

With respect to claim 19, Vona (pages 53 and 55) teaches in situ hybridization analysis of the fetal cells using a chromosome X centromeric probe and thereby teaches "in situ hybridization of a specific probe for a chromosome anomaly of the gender to be detected."

With respect to claim 20, Vona teaches that the maternal blood samples are obtained from women at 11-12 weeks of pregnancy (see page 52).

With respect to claims 21 and 22, Vona (page 52) teaches obtaining 5 ml of maternal blood and diluting the blood 1:10.

With respect to claim 23, Vona teaches that the filter has a pore size of 8 μm (page 52).

With respect to claim 25, Vona (page 52) teaches that the filter is a polycarbonate filter with calibrated ("graded") 8 μm cylindrical graded pores.

7. Claims 1, 2, 19-21 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Kalionis (WO 99/15892; cited in the IDS).

Kalionis teaches a method for prenatal diagnosis of fetal cells isolated from maternal blood. The reference (page 3) states that "(t)he present invention is directed to a method for easily enriching and identifying trophoblast cells in maternal peripheral blood in the presence of a population of blood cell types. The enrichment, identification and analysis of trophoblast cells in peripheral blood provides a means by which non-invasive prenatal diagnosis can be carried out. This method is therefore of particular value in prenatal testing to obtain genetic and/or biochemical information about the fetus."

The method of Kalionis (pages 5-7) comprises the steps of:

a) filtering a sample of maternal blood through a filter according to size, in order to separate fetal cells from maternal blood cells;

b) analyzing the cells retained on the filter by immunostaining for trophoblast-specific markers, in order to confirm the identify of the cells as being of fetal origin (see also page 8);

c) analyzing individual cells by in situ hybridization and immunostaining to demonstrate that the cells are fetal cells (see also pages 10 and 18); and

d) analyzing the individual fetal cells to detect a genetic anomaly or to determine the sex of the fetal cells (see also pages 9-10 and page 21).

With respect to claim 19, the reference (pages 5 and 21-22) teaches that the separated fetal cells are analyzed by in situ hybridization using a probe specific for a chromosomal anomaly or a Y chromosome specific probe.

With respect to claim 20, the reference teaches that the maternal blood samples are obtained form women at 30-37 weeks of pregnancy (see Table 1).

With respect to claim 21, the reference (page 7) teaches obtaining and filtering 5-100 ml of maternal blood.

With respect to claim 23, the reference teaches that the filter has a pore size of 10 μm (page 4), which is within the range of 6 to 15 μm .

8. Claims 26 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Bisconte (U.S. Patent No. 5,306,420).

The claims are drawn to the use of a filtration device for obtaining fetal cells present in maternal blood. The claims do not recite any specific active process steps and thereby have been interpreted as being drawn to any method which utilizes the defined filtration device. Additionally, as noted in the MPEP 211.02, " a preamble is

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generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone.” Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give “life, meaning and vitality” to the claim, “then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation”. In the present situation, the claim language of “for obtaining fetal cells present in maternal blood” is a statement of purpose and intended result and does result in a manipulative difference in the method steps of the claims. Accordingly, the preamble limitation is not accorded patentable weight.

Bisconte (see, e.g., col. 6 and 7 and claim 1) discloses a method for filtering cells wherein the method requires the use of a filtration device comprising:

- a porous filter that can retain cells based on size, wherein the filter is mounted between an upstream and a downstream clamping device;

- a filtration seal (see, also column 8);

- a means for storing or pre-treating samples which is upstream of the filter;

- a perforated gasket facing a storage means which is downstream of the filter;

- and a means for forced filtration (i.e., a pressure device or a suction device).

It is noted that the recitations in claim 27 regarding the applied filtration pressure are not considered to further limit the claim since the claim does not include an active

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step of applying pressure to a filter and does not clearly state how the applied filtration pressure relates to an active process step performed in the recited method.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vona (2002) in view of Fodor (U.S. Patent No. 6,309,822) .

The teachings of Vona are presented above. Vona does not teach detecting a genetic anomaly or genotype using DNA probes attached to a microarray.

However, Fodor teaches methods for detecting mutations and polymorphisms using microarrays wherein a nucleic acid probe comprising a mutation/polymorphism or a wildtype sequence is immobilized onto an array and the array is contacted with a sample nucleic acid (see, e.g., paragraphs 714-716). Fodor (paragraph 368) states that microarrays can be used to simultaneously analyze multiple samples for a large number of genetic markers and allows for simplified, economized and more generally accessible prenatal screening.

In view of the teachings of Fodor, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Vona so as to have detected the genetic mutations or polymorphisms using a microarray in

order to have obtained the advantages set forth by Fodor of providing a method which allowed for the simultaneous analysis of multiple samples and the detection of a plurality of mutations or polymorphisms, thereby providing a faster, more efficient and economical method of prenatal diagnosis.

10. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vona (2002) in view of Pinkel (U.S. Patent No. 6159685).

The teachings of Vona are presented above. Vona teaches prenatal diagnosis of fetal cells by in situ hybridization but does not teach using comparative genomic hybridization (CGH) for prenatal diagnosis.

However, Pinkel (paragraph 41) teaches the method of comparative genomic hybridization and teaches the application of this method to prenatal diagnosis by assaying nucleic acid sequences of fetal cells (see, e.g., paragraphs 8 and 14). Specifically, Pinkel (paragraphs 14 and 41) teaches that CGH employs the methodology of in situ hybridization in order to detect extra or missing copies of whole chromosomes or parts of chromosomes. Pinkel (paragraph 14) states: "(w)hen CGH is applied, for example, in the fields of tumor cytogenetics and prenatal diagnosis, it provides methods to determine whether there are abnormal copy numbers of nucleic acid sequences anywhere in the genome of a subject tumor cell or fetal cell or the genomes from representative cells from a tumor cell population or from a number of fetal cells, without having to prepare condensed chromosome spreads from those cells. Thus, cytogenetic abnormalities involving abnormal copy numbers of nucleic acid sequences, specifically amplifications and/or deletions, can be found by the methods of this invention in the

format of an immediate overview of an entire genome or portions thereof. More specifically, CGH provides methods to compare and map the frequency of nucleic acid sequences from one or more subject genomes or portions thereof in relation to a reference genome. It permits the determination of the relative number of copies of nucleic acid sequences in one or more subject genomes (for example, those of tumor cells) as a function of the location of those sequences in a reference genome (for example, that of a normal human cell)."

In view of the teachings of Pinkel, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Vona so as to have analyzed the isolated fetal cells by CGH in order to have provided a rapid and effective means for identifying genetic anomalies in the fetal nucleic acid, thereby facilitating the method of prenatal diagnosis.

11. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vona (2002).

The teachings of Vona are presented above. Vona does not teach filtering the blood sample through a membrane with a pore density is in the range of " 5×10^4 to 5×10^5 pores/m²" (or 5×10^4 to 5×10^5 pores/cm²).

However, Vona does teach that the blood samples were filtered through a polycarbonate filter calibrated with 8 μ m cylindrical pores. Vona also teaches that cells were concentrated on a 0.6-cm diameter circular spot on the filter and that the cells were laser cut from the filter for collection. At the time the invention was made, it was a property of polycarbonate filters with 8 μ m pores to have a pore density in the range of 5

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10^4 to 5×10^5 pores/cm². Further, to have determined the optimum density of the pores would have been obvious to one of ordinary skill in the art and well within the skill of the art. As discussed in MPEP2144.05(b), "(w)here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 105 USPQ 233, 235 (CCPA 1955). In particular, Vona teaches the criticality of selecting a filter wherein the pore size is sufficient to retain the cell of interest and wherein the pores are spaced sufficiently apart to allow for the separation and isolation of individual cells.

Accordingly, the selection of a filter having an optimum pore density, including a pore density of 5×10^4 to 5×10^5 pores/cm², would have been obvious to one of ordinary skill in the art and well within the skill of the art at the time the invention was made in order to have accomplished the objective of isolating and collecting the single fetal cells, thereby facilitating the method of prenatal diagnosis.

12. Claims 1-7, 9-12, 19-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalionis in view of Vona (American Journal of Pathology. January 2000. 156: 57-63; cited in the IDS).

In particular, with respect to claims 1, 2, 19-21 and 23, it is noted that this rejection is applied to these claims to the extent that the claims are intended to recite in step c) an active step of isolating individual cells.

The teachings of Kalionis are presented above. Kalionis does not teach collecting individual fetal cells by microdissection, wherein the microdissection uses a laser to recover single collected cells in a tube.

However, Vona teaches methods for isolating rare cells from blood wherein the methods comprise passing a blood sample through a filter to retain target cells according to size, analyzing the cells retained on the filter to confirm their identity, using microdissection with the aid of a laser to individually collect the isolated cells retained on the filter into a tube in order to obtain a single collected cell (see pages 58-60). Vona (page 60) teaches that the isolated cells are then lysed and preamplified by PCR prior to genetic analysis using less than one fifth (i.e., 5 out of 60 ul) of the preamplified DNA preparation. It is stated that the use of microdissection to isolate individual cells, followed by the amplified of DNA from the individual cells provides the advantage of a highly sensitive technique for detecting genetic abnormalities (page 58). It is also stated that the method of isolating cells by filtration followed by amplification of the nucleic acids in the isolated cells provided improved results over methods which relied on PCR alone (pages 58 and 62). The method is characterized as being "easy to perform, rapid, and inexpensive" (page 61). The method also provides the advantage of allowing for the isolation of individual cells without damaging the morphology of the cells, thereby providing increased sensitivity (page 61). Additionally, Vona (page 62) states that the method "allows the isolation of large, circulating, nontumorous cells. For example, the isolation of trophoblastic cells from the peripheral blood of pregnant women has been initiated in our laboratory and may constitute an important step toward improving the prenatal diagnosis of genetic diseases."

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have

individually collected the fetal cells by laser microdissection as disclosed by Vona in order to have provided an efficient and effective means for obtaining the individual fetal cells that would allow for the confirmation of the identity of the individual cells and the genetic analysis of the individual cells. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have preamplified the genetic material obtained from the isolated cells in order to have achieved the benefit set forth by Vona of increasing the sensitivity of detection of genetic anomalies in the isolated cells.

With respect to claim 22, Kalionis teaches that the blood can be diluted with an isotonic buffer to reduce the viscosity prior to filtering. Kalionis does not exemplify diluting the blood 10 to 100 fold. However, Vona (page 58) teaches collecting 6 ml of blood and diluting the blood 1:10 in filtration solution prior to filtering. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have diluted the blood 1:10 fold in filtration solution prior to filtering in order to have reduced the viscosity of the blood and thereby to have optimized the filtration process and the isolation of individual fetal cells for prenatal diagnosis.

With respect to claims 23-25, Kalionis does not teach filtering the blood sample through a polycarbonate membrane with a pore density is in the range of " 5×10^4 to 5×10^5 pores/m²" (or 5×10^4 to 5×10^5 pores/cm²). However, Vona (page 58) teaches that the blood samples are filtered through a polycarbonate filter calibrated with 8µm cylindrical pores. Vona also teaches that each sample is filtered through a 0.6-cm

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diameter circular spot on the filter and that the cells were laser cut from the filter for collection. To have determined the optimum density of the pores that would have allowed for the isolation and collection of individual fetal cells would have been obvious to one of ordinary skill in the art and well within the skill of the art. As discussed in MPEP2144.05(b), "(w)here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 105 USPQ 233, 235 (CCPA 1955). In particular, Vona teaches the criticality of selecting an appropriate filter wherein the filter and pore sizes are sufficient to retain the cell of interest and wherein the pores are spaced sufficiently apart to allow for the separation and collection of individual cells. Accordingly, the selection of a polycarbonate filter having an optimum pore density, including a pore density of 5×10^4 to 5×10^5 pores/cm², would have been obvious to one of ordinary skill in the art and well within the skill of the art at the time the invention was made in order to have accomplished the objective of isolating and collecting the single fetal cells, thereby facilitating the method of prenatal diagnosis.

13. Claims 8, 13, 14, 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalionis in view of Vona (2000) and further in view of Bianchi (U.S. Patent No. 5,614,628; cited in the IDS) .

The teachings of Kalionis and Vona are presented above.

With respect to claims 8 and 17, the combined references do not teach analyzing the fetal nucleic acids in order to demonstrate the biparental contribution of fetal DNA.

However, Bianchi teaches methods of prenatal diagnosis wherein the methods are carried out using nucleic acid probes that detect nucleic acids that are specific for both maternally and paternally derived nucleic acid sequences (see, e.g., paragraph 35 and 104-106). In view of the teachings of Bianchi, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have analyzed the fetal nucleic acids for markers specific for each parent in order to have provided a method that would have allowed one to distinguish between female fetal DNA and maternal DNA, thereby confirming the identity of the fetal cells and which would have allowed for the identification of both paternally and maternally inherited sequences in the fetal cells.

With respect to claim 13, the combined references do not teach sequencing the amplified fetal DNA. However, Bianchi (paragraph 31) teaches sequencing amplified fetal DNA in order to detect the presence of genetic variation in the fetal DNA and teaches that sequencing may be used in place of or in addition to detection of genetic variations by PCR or hybridization analysis. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have sequenced the amplified fetal DNA in order to have achieved the benefit of providing a sensitive and effective means for detecting genetic variation in the fetal DNA thereby facilitating the method of prenatal diagnosis.

With respect to claim 14, the combined references do not teach using a probe to analyze the amplified DNA. However, Bianchi (e.g., paragraph 31) teaches that PCR amplified DNA can be analyzed by probe hybridization to detect nucleic acid sequence

variations. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have detected the amplified fetal DNA by probe hybridization in order to have achieved the benefit of providing a sensitive and effective means for detecting genetic variation in the fetal DNA, thereby facilitating the method of prenatal diagnosis.

With respect to claim 16, Kalionis does not specifically teach detecting at least one polymorphism, such a SNP. However, Bianchi teaches methods of prenatal diagnosis which include the detection of polymorphisms, such as that associated with sickle cell anemia (see paragraph 46) and paternally inherited polymorphisms (paragraph 35). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have specifically detected a polymorphism associated with sickle cell anemia in order to have allowed for the prenatal diagnosis of sickle cell anemia or to have specifically detected the paternally inherited polymorphism disclosed by Bianchi in order to have confirmed the identity of female fetal cells and to have distinguished female fetal cells from maternal cells.

14. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kalionis in view of Vona (2000) and Fodor (U.S. Patent No. 6,309,822) .

The teachings of Kalionis and Vona are presented above. The combined references do not teach detecting a genetic anomaly or genotype using DNA probes fixed to a microarray.

However, Fodor teaches methods for detecting mutations and polymorphisms using microarrays wherein a nucleic acid probe comprising a mutation/polymorphism or a wildtype sequence is immobilized onto an array and the array is contacted with a sample nucleic acid (see, e.g., paragraphs 714-716). Fodor (paragraph 368) states that microarrays can be used to simultaneously analyze multiple samples for a large number of genetic markers and allows for simplified, economized and more generally accessible prenatal screening.

In view of the teachings of Fodor, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have detected the genetic mutations or polymorphisms using a microarray in order to have obtained the advantages set forth by Fodor of providing a method which allowed for the simultaneous analysis of multiple samples and the detection of a plurality of mutations or polymorphisms, thereby providing a faster, more efficient and economical method of prenatal diagnosis.

15. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kalionis in view of Vona (2000) and Pinkel (U.S. Patent No. 6159685).

The teachings of Kalionis and Vona are presented above. Kalionis teaches prenatal diagnosis of fetal cells by in situ hybridization but does not teach using comparative genomic hybridization (CGH) for prenatal diagnosis.

However, Pinkel (paragraph 41) teaches the method of comparative genomic hybridization and teaches the application of this method to prenatal diagnosis by assaying nucleic acid sequences of fetal cells (see, e.g., paragraphs 8 and 14).

Specifically, Pinkel (paragraphs 14 and 41) teaches that CGH employs the methodology of in situ hybridization in order to detect extra or missing copies of whole chromosomes or parts of chromosomes. Pinkel (paragraph 14) states: "(w)hen CGH is applied, for example, in the fields of tumor cytogenetics and prenatal diagnosis, it provides methods to determine whether there are abnormal copy numbers of nucleic acid sequences anywhere in the genome of a subject tumor cell or fetal cell or the genomes from representative cells from a tumor cell population or from a number of fetal cells, without having to prepare condensed chromosome spreads from those cells. Thus, cytogenetic abnormalities involving abnormal copy numbers of nucleic acid sequences, specifically amplifications and/or deletions, can be found by the methods of this invention in the format of an immediate overview of an entire genome or portions thereof. More specifically, CGH provides methods to compare and map the frequency of nucleic acid sequences from one or more subject genomes or portions thereof in relation to a reference genome. It permits the determination of the relative number of copies of nucleic acid sequences in one or more subject genomes (for example, those of tumor cells) as a function of the location of those sequences in a reference genome (for example, that of a normal human cell)."

In view of the teachings of Pinkel, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kalionis so as to have analyzed the isolated fetal cells by CGH in order to have provided a rapid and effective means for identifying genetic anomalies in the fetal nucleic acid, thereby facilitating the method of prenatal diagnosis.

16. Claims 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bisconte (U.S. Patent No. 5,306,420) in view of Bisconte (FR 2782730; cited in the IDS; note that the English translation of this document is US 2002/0028431; see page 1 of the FR 272730 document as filed)

The teachings of Bisconte ('420) are presented above.

With respect to claims 28 and 29, Bisconte teaches that the filter may be 0.6um for filtering bacteria and that the pore size of the filter is varied depending on the size of cell that is to be isolated (see col. 8). Bisconte does not teach that the membrane has a pore size of 8 um.

However, Bisconte (FR 272730) teaches methods of using a filtration device to isolate rare, pathogenic cells from blood, wherein the filter may have a pore size of between 5 and 10 um, and preferably the pore size is 8 um (see pages 2 and 3). It is stated that the filter is adapted to the size of the target cells (pages 5-6) . Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Bisconte ('420) so as to have used a filtration device having a pore size of 5-10 um and preferably 8 um in order to have achieved the advantage of providing an effective method for isolating and collecting rare pathogenic cells present in blood samples.

Further, Bisconte ('420) does not teach that the membrane has a pore density of 5×10^4 to 5×10^5 pores/cm². However, Bisconte (FR 272730) teaches that the filtration device is used to isolate and collect single cells. To have determined the optimum density of the pores that would allow for the isolation and collection of single cells from

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the filter membrane would have been obvious to one of ordinary skill in the art and well within the skill of the art. As discussed in MPEP2144.05(b), "(w)here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 105 USPQ 233, 235 (CCPA 1955). In particular, Bisconte teaches the criticality of selecting a filter wherein the pore size is sufficient to retain the cell of interest and wherein the pores are spaced sufficiently apart to allow for the separation and isolation of individual cells. Accordingly, the selection of a filter having an optimum pore density, including a pore density of 5×10^4 to 5×10^5 pores/cm², would have been obvious to one of ordinary skill in the art and well within the skill of the art at the time the invention was made in order to have accomplished the objective of isolating and collecting the single pathogenic cells, thereby facilitating the method of diagnosis.

With respect to claim 27, this rejection is based on the interpretation that the claim is intended to recite an active process step of applying a filtration pressure of 0.05 to 0.8 bars. Bisconte ('420) does not state the specific pressure that is applied to the filter in order to facilitate passage of fluids through the filter and retention of the target cells on the filter. However, Bisconte (FR 272730; page 4 and 5) teaches the use of a filtration device to isolate rare pathogenic cells, wherein the filtration device has a partial vacuum of approximately 50,000 PA (i.e., 0.5 bars) under the filter. Further, the selection of an optimal filtration pressure based on the type and size of cell to be isolated was well within the skill of the art at the time the invention was made. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the

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invention was made to have modified the method of Bisconte ('420) so as to have used a filtration pressure of 50,000 PA in order to have accomplished the objective set forth by Bisconte (FR 272730) of providing an effective method for isolating and collecting rare pathogenic cells from blood samples in a manner sufficient to maintain the integrity of the cell and to have allowed for the isolation of individual cells.

17. The art made of record and not relied upon is considered pertinent to applicant's disclosure.

Sterlitech discloses polycarbonate membranes having a pore size of 8 μm and a pore density of 1×10^5 pores/ cm^2 .

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)-272-0745.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

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Carla Myers

October 24, 2005


CARLA J. MYERS
PRIMARY EXAMINER